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## **What's new in pediatric acute pain therapy?**

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**Abstract:** **PURPOSE OF REVIEW** This review highlights the current trends of efficient and safe perioperative pediatric pain therapy in the context of a multimodal pain therapy concept. **RECENT FINDINGS** A multimodal pain therapy concept should be easy to apply and safe regarding the occurrence of side-effects. The administration of nonopioid analgesics should be obligatory, regional anesthesia techniques - under ultrasound guidance - should be performed whenever possible, opioids should be given immediately and sufficiently whenever necessary, the administration of co-analgesics like lidocaine, dexamethasone or ketamine should be considered, and most importantly, each pain therapy should be performed according to pain assessment and long enough until adequate pain relief. **SUMMARY** Safe and simple pediatric pain management in the perioperative period combines not only easy to apply and safe stepwise pain therapy itself, but also adequate pain assessment and the implementation of continuous hospital quality improvement strategies.

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# What's new in pediatric acute pain therapy?

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## Purpose of review

This review highlights the current trends of efficient and safe perioperative pediatric pain therapy in the context of a multimodal pain therapy concept.

## Recent findings

A multimodal pain therapy concept should be easy to apply and safe regarding the occurrence of side-effects. The administration of nonopioid analgesics should be obligatory, regional anesthesia techniques – under ultrasound guidance – should be performed whenever possible, opioids should be given immediately and sufficiently whenever necessary, the administration of co-analgesics like lidocaine, dexamethasone or ketamine should be considered, and most importantly, each pain therapy should be performed according to pain assessment and long enough until adequate pain relief.

## Summary

Safe and simple pediatric pain management in the perioperative period combines not only easy to apply and safe stepwise pain therapy itself, but also adequate pain assessment and the implementation of continuous hospital quality improvement strategies.

## Keywords

analgesia, opioids, pain, pain therapy, pediatric anesthesia, pediatrics, regional anesthesia

## INTRODUCTION

'Pediatric patients seldom need relief of pain after surgery, they tolerate discomfort well' [1]. In 1968, this comment of Swafford and Allen about the management of postoperative pain in children unfortunately resulted in poor pain control and slow development of sufficient pediatric postoperative pain therapy during the following decades. Thirty years ago, Mather and Mackie [2] reported that still 40% of postoperative children experienced moderate or severe pain and that 75% had insufficient perioperative analgesia prescribed or applied. Significant painful stimulation without adequate analgesia will not only cause unacceptable pain at the time of intervention, it will produce long-lasting pain memory and behavioral disorders [3–5]. The structural components necessary to perceive pain are already present at about 25 weeks of gestation, so that even our smallest patients are able to show a graded stress response to any painful stimulation [6–9]. Although there have been several advantages in intraoperative and postoperative analgesia in infants and children during the past years, acute pain is still often undertreated due to lack of comprehensive acute perioperative pain management concepts, inadequate pain assessment [10<sup>11</sup>,12], insufficient knowledge about

age-specific aspects of physiology and pharmacology, and the fear of adverse events [13].

Even if it appears that pediatric analgesic use still remains significantly less than that for adults, a range of safe and effective pain therapy concepts have been developed [10<sup>11</sup>]. The aim of this review is to illustrate several new important tools for daily clinical practice to further improve pain relief in the acute perioperative setting of pediatric surgery.

## WHAT ARE THE MOST PAINFUL PROCEDURES?

The most common surgical interventions during childhood are simultaneously the most painful in

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## KEY POINTS

- Acute perioperative pain in infants and children is still often undertreated, although there have been several advantages in intraoperative and postoperative analgesia during the past decades.
- A modern multimodal perioperative pain therapy concept must be easy to apply and safe regarding the occurrence of side-effects.
- To optimize therapy strategies and to improve the quality of postoperative pain management, the implementation of pain assessment and continuous quality improvement strategies is highly recommended.

context to their low surgical invasivity. Tonsillectomy, appendectomy, orchidopexy, and orthopedic procedures are described to be more painful than expected [14]. The pain intensity on the first day after surgery has recently been investigated in over 50 000 patients and published by Gerbershagen *et al.* [15<sup>22</sup>]. Surprisingly, beneath the high pain scores after orthopedic surgery, tonsillectomy and appendectomy are associated with quite similar pain scores. Up to 44% of children suffered from severe pain [visual analog scale (VAS) >5] after tonsillectomy on the third postoperative day, and up to 30% on day 7 [16]. Another publication described similar pain scores during the first 7 days after tonsillectomy, with many children still experiencing clinically significant levels of pain throughout the second week of recovery [17<sup>23</sup>].

Orchidopexy was also unexpectedly associated with higher pain scores and more prolonged pain [17<sup>23</sup>,18] than – for instance – herniotomy. Pain after appendectomy is comparable to tonsillectomy, with the laparoscopic approach being at least as painful as the open procedure [14].

## NEW CONCEPTS

There is still a lack of sufficient and adequate pain relief not only on the day of surgery but also during the first postoperative days. To counteract pain in the immediate postoperative period in infants and children, an adequate multimodal pain therapy concept for daily clinical practice must be implemented. It should be easy to apply and safe regarding the occurrence of side-effects. Local or regional anesthesia should be performed whenever possible, the administration of nonopioid analgesics should be obligatory after each kind of painful intervention or surgery, opioids should be given immediately and sufficiently whenever necessary, the administration of co-analgesics should be considered, and most

importantly, each pain therapy should be performed according to pain assessment and long enough until adequate pain relief. Figure 1 shows an example for multimodal pain therapy in typical pediatric surgical procedures ('take home receipts').

## REGIONAL ANESTHESIA

The benefit of additional local and regional anesthesia for pediatric surgery is a well known concept. Pediatric regional anesthesia combined with general anaesthesia is a standard in pediatric anesthesia to reduce intraoperative opioids and to provide postoperative pain relief in infants and children. Two large studies underline the safety of this concept, so that every child undergoing a surgical intervention accessible to any kind of regional anesthesia should get this technique. Polaner *et al.* [19] evaluated in a multi-institutional study in the USA approximately 15 000 regional blocks in pediatric patients. There were no deaths or complications with sequelae lasting for more than 3 months. Single injection blocks as well as peripheral techniques had lower complication rates than continuous blockades and central regional anesthesia techniques. Ninety-five per cent of all blocks were performed under general anesthesia. Ecoffey *et al.* [20] described nearly 30 000 regional blocks also performed under general anesthesia in a 1-year follow-up survey in Europe. The documented complications (0.12%) were usually minor and also did not result in any sequelae. The complication rate was six times higher for central than for peripheral blocks.

Regional anesthesia may safely be administered not only under general anesthesia but also under sedation with spontaneous respiration. Caudal blockade can be performed for all kinds of subumbilical pediatric surgery under sedation with excellent results concerning high success and very low complication rates [21]. Infants under 1 year normally do not require additional sedation after successful caudal block. In an Austrian study, 76.3% of all patients were adequately pain and stress-free after caudal blockade and did not require further sedative medication during surgery. Ultrasound guidance is a very helpful tool for peripheral blocks, like transversus abdominis plane (TAP) block, which may be a perfect alternative for pain management of several minor abdominal surgery interventions, if the patient's age is over 10–12 years and therefore caudal blockade not feasible [22]. Sahin *et al.* [23] recently compared TAP block with wound infiltration in 57 children. TAP block provided prolonged postoperative analgesia and reduced analgesic use without any clinical side-effects after inguinal hernia repair [23]. Continuous epidural catheterization

Take home receipts
<b>Pediatric surgery, pediatric urology surgery</b> Caudal block including clonidine 2–3 g/kg in patients from 3 months of age Metamizol 20 mg/kg at the end of surgery, max 60 mg/kgBW/24h
<b>Appendectomy</b> Caudal block if possible, alternatively lidocaine i.v. 1.5 mg/kg after induction of anesthesia, 1.5 mg/kg/h during surgery and the first postoperative hours (monitoring of ECG, blood pressure and SpO <sub>2</sub> obligatory) Metamizol 20 mg/kg at the end of surgery, max 60 mg/kgBW/24h
<b>Tonsillectomy</b> Intraoperatively supplementary clonidine 2 g/kg i.v. and dexamethasone 0.15 mg/kg i.v. (max. 4 mg) Metamizol 20 mg/kg at the end of surgery, max 60 mg/kgBW/24 h + Ibuprofen 10 mg/kg (4x/d)
<b>Rescue medication</b> If a light to moderate analgesic is sufficient: nalbuphine 0.1–0.2 mg/kg i.v. (single dose), 0.1–0.2 mg/kg/h (continuously i.v.) If a strong opioid is needed: morphine or piritramid 0.025–0.05–0.1 mg/kg i.v. (single dose). For patient controlled analgesia: 25 g/kg (bolus), 2–4–10 g/kg/h continuously.

**FIGURE 1.** ‘Take home receipts’ for perioperative multimodal pain therapy in typical pediatric surgical procedures.

under general anesthesia should only be performed by experienced anesthesiologists in specialized centers when major thoracic, abdominal or orthopedic perlvic surgery is planned and sufficient postoperative analgesia is needed the following days [24]. Upper extremity blocks for orthopedic and trauma surgery under ultrasound guidance are also performed under sedation in some institutions [25,26].

## NEW SYSTEMIC PAIN THERAPY CONCEPTS

Systemic analgesia with paracetamol, metamizol and NSAIDs is the basis of every kind of analgesia during any painful procedure. The dosage regimen as well as the benefits and pitfalls of these drugs were extensively described in a magnitude of publications, recently also in an excellent review of perioperative analgesia in pediatric surgery in this Journal [10<sup>\*\*\*</sup>]. As a small summary of its daily administration, the authors administer in their institution – as in several children hospitals in Europe – ibuprofen 10 mg/kg body weight orally or rectal up to 4 times/day, metamizol 20 mg/kg body weight orally or intravenously up to 3 times/day, diclofenac 1 mg/kg body weight orally, rectal or intravenously (over 6 years of age) up to 3 times/day, and paracetamol up to 7.5–15 mg/kg body weight orally, rectal or intravenously up to 4 times/day (depending on patient’s age) [27,28]. It can be considered to administer paracetamol, metamizol or NSAIDs as a preventive medication before the start of surgery and as a proactive approach continuously

during the whole immediate period until complete pain relief. Paracetamol has the lowest analgesic effect in comparison to diclofenac, as described in a study concerning the opioid-sparing effects of both drugs [29]. Diclofenac did reduce morphine consumption after appendectomy, but the co-administration of paracetamol did not improve this effect. In contrast to these results, Mireskandari *et al.* advise the combination of both to be more effective than placebo or both substances alone. Diclofenac was more effective than paracetamol. These results were underlined by Elia *et al.*, who analyzed data from 52 randomized placebo-controlled trials in adults, and evidenced that the combination of NSAIDs with opioids offer some advantages of the use of opioids alone. The overall morphine consumption was decreased up to 55%, and also the incidence of nausea and vomiting and sedation. Ibuprofen was described as more effective than paracetamol for the management of pain in adults and children by a large meta-analysis of 85 studies [30]. Important to know is that ibuprofen can be applied from 4th month of life/6 kg of body weight (rectally and orally as suspension), whereas diclofenac is registered for children only from 1 year of age.

If systemic nonopioid analgesics alone or in combination with regional anesthesia do not provide sufficient postoperative analgesia, the addition of a light to moderate opioid analgesic is necessary. The availability of appropriate and safe substances is rare: during the past years, deaths were reported following tonsillectomy in children due to the administration of intravenous opioids [31]. Genetic

variations in the liver microenzyme, CYP2D6, had been associated with this fatal adverse event. Opioids metabolized by CYP2D6 include codeine, tramadol, hydrocodone, and oxycodone. Ultrarapid metabolizers and some extensive metabolizers of CYP2D6 produce more active opioid metabolites resulting in life-threatening adverse effects. Young and obese children with a history of sleep apnea are at a higher risk of developing serious opioid-related respiratory depression. Therefore, codeine is not further recommended for the administration in young children [32]. The Pharmacovigilance Risk Assessment Committee (PRAC) endorses the US Food and Drug Administration (FDA) recommendation [33<sup>■</sup>] that codeine has only to be used to treat acute (short-lived) moderate pain in children above 12 years of age [34<sup>■</sup>,35,36]. Furthermore, codeine should not be used at all in children (aged below 18 years) who undergo surgery for the adenectomy or tonsillectomy, as well as in patients with obstructive sleep apnea, because these patients are more susceptible to respiratory problems. Tramadol, another light-to-moderate opioid, has the same risk profile, even if no deaths are described until now [37]. Due to this reason and its disagreeable side-effects like nausea and vomiting, it is also not further recommended for pain management in the immediate perioperative setting.

## NALBUPHINE

Nalbuphinehydrochloride [(2)-17(cyclobutylmethyl)-4,5a-epoxymorphinan-3,6a,14-triol hydrochloride] is a light to moderate, semisynthetic opioid analgesic, which acts predominately as an agonist at the  $\kappa$ -receptor and as an antagonist at the  $\mu$ -receptor [38]. Its  $\kappa$ -receptor agonism results in additional considerable sedation, which is a desirable co-effect in pediatric pain therapy, when pain is associated with agitation, when postoperative immobilization is required, or when other causes of discomfort cannot be excluded. Nalbuphine is only available for intravenous administration. It can be

administered as a bolus, a continuous infusion, and patient-controlled analgesia. Nalbuphine is the nearly ideal opioid for safe pediatric postoperative pain therapy due to its unique pharmacological properties and its high safety profile: its analgesic potency is comparable with that of morphine. Its 'ceiling effect' disables on one hand a further enhancement of analgesia above 0.3–0.4 mg/kg body weight, and on the other hand, this inhibits the occurrence of central respiratory depression [39]. Niesters *et al.* [34<sup>■</sup>] recently reviewed all case reports between 1981 and 2012 concerning respiratory depression in pediatrics. Fourteen children between 17 days and 12 years old were documented. Central respiratory depression occurred after codeine and morphine, but not after nalbuphine administration. Even a 10-fold accidental overdose did not result in clinically relevant respiratory depression [40,41]. This fact emphasizes the safety of the substance for pediatric pain therapy. Another benefit is that nalbuphine is not listed in the narcotics law of Austria, Germany and Switzerland, so it can be easily administered also by nurses on the normal ward without delay in case of immediate pain therapy necessity. A commonly recommended dosage regimen is shown in Table 1.

## CO-ANALGESICS

Lidocaine, ketamine, and dexamethasone may be added as co-analgesics to each pain therapy concept.

### Lidocaine

Another new concept is the co-administration of intravenous lidocaine during anesthesia to reduce postoperative pain intensity and intraoperative opioid consumption. Lidocaine has been considered as well tolerated for intravenous use because of its long history of systemic administration as an anti-arrhythmic drug [42]. McCarty *et al.* considered in their review of 16 trials and 395 patients lidocaine to be well tolerated and advantageous in adult abdominal surgery. Thirteen of these trials

**Table 1.** Nalbuphine, intravenous dosage regimen

Preoperative	Preoperative pain: fractures	0.1–0.2 mg/kg
Intraoperative	Short and less painful procedures	0.2 mg/kg
Postoperative	Bolus dose repetition every 3–4 min	0.1–0.2 mg/kg (max. 0.3–0.4 mg/kg); single bolus dose max. 5 mg (dysphoria)
	Continuously (until 6–8 years of age)	0.1 (–0.2) mg/kg/h
	PCA (over 6–8 years of age)	Continuously 0.02 mg/h basal rate; bolus dose 0.02 mg/kg; lock out 5 min. Not more than 18 bolus doses/2 h; cumulative not more than 0.4 mg/kg

All dosages are mg/kg body weight. PCA, patient-controlled analgesia.



demonstrated preventive analgesia by intravenous lidocaine, not associated with a specific regimen or dosage.

Until now, lidocaine is only investigated in children in the laryngeal reflex responses to tracheal intubation [43], and as an adjunct to propofol to prevent or reduce injection pain [44,45]. However, the low-dose co-administration of lidocaine intravenously is a promising concept to further reduce postoperative pain therapy requirements, for example, in children with open appendectomy, when caudal block is not possible or contraindicated.

### Ketamine

The N-methyl-D-aspartate antagonist ketamine is often used as an adjunct to reduce pain severity, even if the evidence for an opioid-sparing effect in children is less clear, as described recently in the review of Russell *et al.* [10<sup>22</sup>,46]. Dahmani *et al.* [47] who investigated 35 randomized, blinded controlled studies, supported these results. The authors described that systemic ketamine is effective in decreasing postoperative pain intensity and analgesic requirements, but failed to influence early (6–24 h) pain intensity and analgesic requirement. Whereas ketamine, administered locally, decreased immediate and early pain intensity and analgesic requirements, it failed to exhibit a postoperative opioid-sparing effect [47].

### Dexamethasone

Dexamethasone is frequently used in the perioperative setting to reduce the incidence of nausea and vomiting [48]. A meta-analysis of 24 randomized controlled trials in 2751 patients emerged several important findings [49<sup>23</sup>]: single-shot intermediate-dose dexamethasone (0.11–0.2 mg/kg) has opioid-sparing effects in adults. It also reduces early and late pain, but heterogeneity was partially explained by the time of drug administration (preoperative vs. intraoperative). High-dose dexamethasone (more than 0.2 mg/kg) had opioid-sparing effects and also decreased pain scores, whereas it was unable to detect a difference in opioid use for the low-dose dexamethasone (less than 0.1 mg/kg) when given intraoperatively despite a reduction in late pain at rest and at movement. Therefore, a single perioperative systemic dexamethasone dose is evidenced to be used as part of a multimodal pain strategy.

## PEDIATRIC POSTOPERATIVE QUALITY ANALYSIS

To focus treatment and to improve the quality of postoperative pain therapy, the implementation of continuous quality improvement strategies has

been recommended [50]. In light of this, a web-based Germany-wide outcome-oriented project called Quality Improvement in Postoperative Pain Management (QUIPS) was developed in 2005, consisting of standardized data acquisition and an analysis of quality and process indicators [14,51]. QUIPS has clearly shown that outcomes in postoperative pain therapy are measurable and comparable as well as leading to improved care. As a consequence, an equivalent tool was recently developed for children called Quality Improvement in Postoperative Pain Management in Infants (QUIPSI) [52]. QUIPSI is validated in a multicenter trial in 10 German hospitals. It was shown that children at least 4 years of age normally can complete the questionnaire [53]. The results of QUIPSI uncover gaps in the postoperative pain management which will help improve the quality in the postoperative setting. The QUIPSI approach should be integrated as a daily tool into all pediatric surgical departments [28]. The German project has now been transferred to a European project, called 'Improvement in postoperative PAIN Outcome' ('PAIN-OUT'). The overall goal is to improve clinical care of patients with postoperative pain, in developed as well as in developing countries. This is achieved by collecting patient-reported pain outcomes as well as clinical data in a standardized procedure, using a questionnaire available in 18 languages. Participating hospitals subsequently receive online feedback about their results and benchmarking with other hospitals. Longitudinal records allow follow-up of changes over time ([www.pain-out.eu](http://www.pain-out.eu)).

## CONCLUSION

A modern multimodal pain therapy concept for the immediate postoperative period in infants and children should be easy to apply and well tolerated regarding the occurrence of side-effects. The administration of nonopioid analgesics has to be obligatory, additional local and regional anesthesia techniques-preferable under ultrasound guidance-should be performed whenever possible, opioids should be given immediately and sufficiently, the administration of co-analgesics should be considered, and most importantly, each pain therapy should be performed according to pain assessment and long enough until adequate pain relief.

To focus therapy strategies and to improve the quality of postoperative pain management, the implementation of continuous quality improvement strategies is recommended. Several web-based programs have been implemented in the European Union.

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## Conflicts of interest

There are no conflicts of interest.

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Essential information about codeine and its pharmacokinetic profile.

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